Neurobiology of Aging 35 (2014) S29–S34

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Review

Amyloid-β diurnal pattern: possible role of sleep in Alzheimer's disease pathogenesis

Brendan P. Lucey [a,*], Randall J. Bateman [a,b,c]

[a] Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA
[b] Knight Alzheimer's Disease Research Center, Washington University School of Medicine, St. Louis, MO, USA
[c] Hope Center for Neurological Disorders, Washington University School of Medicine, St. Louis, MO, USA

ARTICLE INFO

Article history:
Received 25 October 2013
Received in revised form 9 March 2014
Accepted 13 March 2014
Available online 15 May 2014

Keywords:
Alzheimer's disease
Amyloid-β
Sleep
Diurnal pattern

ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline that is a growing public health crisis with a prevalence projected to more than double in the next 20 years. Sleep is frequently impaired in individuals with AD. Further, recent studies have linked numerous age-related sleep disturbances such as poor sleep efficiency and sleep apnea, to future risk of cognitive impairment. Aggregation of amyloid-β (Aβ) into extracellular plaques in the brain is a key step in AD pathogenesis and likely begins 20 years before the onset of dementia. Aβ concentrations in both humans and mouse models show Aβ concentrations rise during wakefulness and fall during sleep, that is, an Aβ diurnal pattern. There is evidence in animal models that changes in sleep time alter Aβ deposition, suggesting that sleep may play a role in AD pathogenesis. A hypothetical model for the role of sleep and the Aβ diurnal pattern in AD pathogenesis is proposed.

© 2014 Elsevier Inc. All rights reserved.

1. Amyloid-β and Alzheimer's disease pathogenesis

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive impairment that is a current and growing public health crisis that only has minimally effective treatments. In 2010, more than 5 million Americans aged ≥65 years were living with AD, and this number is expected to increase to 13.5 million in 2050 (Alzheimer's Association, 2010). A reliable, even modest reduction in the risk of AD would have a tremendous public health impact. Age is the greatest risk factor for AD, but the progression to cognitive impairment likely results from genetic (e.g., ApoE4) and environmental (e.g., exercise, diet, and sleep) factors that influence AD pathology (Mayeux and Stern, 2012). Recent evidence in both humans and animal models suggests a possible mechanism through which sleep, likely interacting with other genetic and environmental risk factors, may play a role in AD pathogenesis.

Deposition of extracellular amyloid-β (Aβ) into insoluble plaques in the brain is a key early step in the pathogenesis of AD that is associated with the aggregation of tau into intracellular neurofibrillary tangles, synaptic dysfunction, neuronal loss, and cognitive impairment (Hardy and Selkoe, 2002; Jack et al., 2010). The Aβ peptide is predominantly produced in the brain by neurons when amyloid precursor protein (APP) is cleaved by β- and γ-secretases into multiple isoforms of different amino acid lengths (Strooper et al., 2010). More specifically, γ-secretase cuts the C-terminal end of the Aβ peptide to generate 3 major isoforms, that is, Aβ38, Aβ40, and Aβ42. Aβ isoforms are then secreted into the interstitial fluid (ISF) through synaptic vesicle exocytosis, which is a process influenced by synaptic activity (Cirrito et al., 2005). The contribution of Aβ isoforms to plaque formation varies. Whereas Aβ40 is produced at higher concentrations, Aβ42 is more hydrophobic, neurotoxic, and prone to aggregate (Jarrett et al., 1993). Further, the aggregation of Aβ into extracellular plaques has been found to be concentration dependent. In a mouse model study, neural cells were transplanted from APP23 transgenic mice into wild-type mice and Aβ levels were measured both within the neural graft and the surrounding ISF. Aβ concentrations were the highest within the graft and decreased as a function of the distance from the graft, and a similar gradient pattern was observed for amyloid plaques (Meyer-Luehmann et al., 2003). Since all the Aβ deposition did not occur only within the grafts, it was suggested that Aβ diffusion into surrounding neural tissue played a role in plaque formation.

Neuropathologic changes in AD, that is, extracellular amyloid plaques and intracellular neurofibrillary tangles of aggregated

* Corresponding author at: Department of Neurology, Washington University School of Medicine, Campus Box 8111, 660 South Euclid Ave, St. Louis, MO 63110, USA. Tel.: +1 314 362 4342; fax: +1 314 747 3813.
E-mail address: luceyb@neuro.wustl.edu (B.P. Lucey).

0197-4580/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2014.03.035

tau, likely proceed in a sequential anatomic pattern involving the entorhinal cortex, hippocampus, and medial temporal lobe (Braak and Braak, 1991). Aβ deposition is probably insufficient to result in cognitive decline because pathologic studies show that significant neuronal and synaptic loss has already occurred by the time clinical symptoms manifest. Further, amyloid deposition can be assessed in vivo in humans by positron emission tomography (PET) with an amyloid tracer, that is, Pittsburgh Compound B (PiB) that binds to amyloid, or by decreased cerebrospinal fluid (CSF) Aβ42 concentrations. Approximately 25%–30% of individuals in their eight decade who were cognitively normal that were assessed by either of these methods have been found to have amyloid deposition (Mintun et al., 2006; Morris et al., 2009). The period of amyloid deposition with normal cognitive functioning has been described as "preclinical Alzheimer's disease" (Jack et al., 2010; Sperling et al., 2011). Treatment of AD is hypothesized to be the most successful in this preclinical phase before Aβ deposition into Aβ-containing plaques and tau aggregation occurs, which causes significant cell loss leading to the onset of clinically detectable cognitive impairment (Morris, 2005).

Amyloid imaging has also shown that Aβ deposition co-localizes anatomically with other imaging abnormalities associated with AD in many regions of the brain. Abnormalities that co-localize with PiB-PET include brain atrophy as shown on brain magnetic resonance imaging, hypometabolism measured by fluorodeoxyglucose-PET, and dysfunction of the default mode network (DMN) as measured by functional magnetic resonance imaging (Bero et al., 2011; Buckner et al., 2005). The DMN is the resting state network most active in the absence of task performance (Raichle et al., 2000) and has been reported as the first network affected by AD (Greicius et al., 2004). The DMN is associated with episodic memory (Buckner, 2004), which is a cognitive domain that is impaired early in AD. Since the DMN is a resting state network and is therefore synaptically and metabolically more active than other regions of the brain, this co-localization with AD pathology may be because of increased Aβ production and secretion into the ISF resulting in a higher local concentration and greater deposition. Additionally, decreased energy metabolism and atrophy in the brain have also been correlated with areas of amyloid deposition (Vlassenko et al., 2010). Because all these imaging abnormalities overlap, these findings suggest that increased synaptic activity leading to Aβ aggregation into plaques progresses to decreased neuronal metabolic function and atrophy presumably through neuronal loss. This hypothesis is supported by findings in the dominantly inherited AD population (Bateman et al., 2012).

2. Sleep and AD

Sleep serves a restorative function in the brain and is involved with memory retention. More specifically, slow-wave sleep (SWS) plays a critical role in the consolidation of long-term memory (Born and Wilhelm, 2012). Good quality sleep involves following a day and/or night (i.e., diurnal) pattern of alertness and activity during the day followed by quiescence at night. Cycling several times through the different sleep stages during the sleep period is also essential to restorative sleep. Scoring an individual as awake or in a specific sleep stage is primarily determined by changes on an electroencephalogram (EEG) recorded during polysomnography. In the awake state, the EEG shows low amplitude, high-frequency fluctuations because of neurons in the cerebral cortex firing irregularly. As wakefulness gives way to sleep, the low amplitude, high-frequency activity attenuates as cortical neurons undergo a slow oscillation ($<$1 Hz) in membrane potential between a hyperpolarized state with no neuronal firing to a depolarized state of intense firing (Massimini et al., 2004). This slow oscillation is the fundamental cellular process that organizes waveforms seen on EEG during sleep, that is, sleep spindles and slow waves.

There are 4 sleep stages. The EEG background in rapid eye movement sleep is similar to the awake state with low amplitude, mixed-frequency activity. Non-rapid eye movement (NREM) sleep is characterized by 3 stages that exhibit progressively increased slow wave activity (SWA): N1 or drowsiness, N2, and N3 or SWS. During the deeper stages of NREM sleep (N2 and N3) there are more high-amplitude slow waves, which likely accounts for the general decrease in regional synaptic activity during NREM sleep (Vyazovskiy et al., 2011). These periods of deeper NREM sleep with increased SWA are hypothesized to decrease synaptic strength to a level that is energetically sustainable and promotion of synaptic plasticity and memory (Tononi and Cirelli, 2006).

Nearly all people older than the age of 60 years have disrupted sleep architecture and decreased SWS (Redline et al., 2004). Further, aging has also been associated with regional brain atrophy involving the midline frontal lobe regions (Sowell et al., 2003) and cognitive decline (Buckner, 2004). These 3 factors have been independently associated with aging. However, a recent study found that age-related medial prefrontal cortex gray-matter atrophy was associated with reduced NREM SWA in older adults, the extent of which statistically accounted for the impairment of overnight sleep-dependent memory retention (Mander et al., 2013). These recent findings suggest an additional potential mechanism that may be linked to the sleep changes that have been observed in aging that may be contributing to cognitive decline in older individuals.

Sleep disturbances in individuals with AD are multifaceted and include increased or decreased total sleep time, nocturnal arousals, and reversal of the day and/or night sleep pattern (McCurry et al., 1999). However, these sleep disturbances have been measured in individuals already exhibiting cognitive impairment and are likely a manifestation of dementia. Sleep interventions at this stage of AD may be difficult to both implement and achieve positive benefits. For example, the incidence of sleep disorders (e.g., sleep apnea) is increased in patients with AD and continuous positive airway pressure (CPAP) therapy may slow or improve cognitive functioning in patients with AD and sleep disordered breathing (SDB) (Ancoli-Israel et al., 2008; Cooke et al., 2009). However, both the diagnosis and treatment of sleep disorders (e.g., SDB) in patients with AD is challenging because of the patients' underlying cognitive dysfunction impeding both the diagnosis via polysomnography and treatment with CPAP. Therefore, the efficacy of current therapies (e.g., CPAP) is difficult to assess in an AD patient population (Yesavage et al., 2003).

Recent research has focused on the risk of developing cognitive impairment in cognitively-normal individuals with long-term sleep disturbances. In multiple cross-sectional studies, changes in sleep duration have been associated with an increased risk of cognitive impairment. Tworoger et al. (2006) observed that self-reported difficulty sleeping and sleep duration $\leq$5 hours/night in older women was associated with poorer cognitive performance for general cognition, verbal memory, category fluency, and attention. Others have shown conflicting results including cognitive impairment associated with longer sleep times $>$11 hours/night (Faubel et al., 2009) or $\geq$9 hours/night (Loerbroks et al., 2010), but not short sleep time or both short and long sleep time (Ferrie et al., 2011; Kronholm et al., 2009; Xu et al., 2011). Additional markers of poor sleep quality, that is, low sleep efficiency, prolonged sleep latency, increased wake after sleep onset, and increased napping, have all been associated with impaired cognitive function (Blackwell et al., 2006, 2011; Keage et al., 2012; Potvin et al., 2012).

Changes in circadian rhythm activity measured by actigraphy and calculated using cosinor analysis for mesor, amplitude, and acrophase of the sleep-wake cycle are associated with the risk of dementia in older women (Tranah et al., 2011). Specifically, the mesor is the midline of the oscillation corresponding to the circadian activity, the amplitude is the distance between the peak and the mesor, and the acrophase is the time corresponding to the peak of the curve (Fig. 1). In this study, declining amplitude of the sleep-wake cycle, which signifies the strength of the rhythm based on the difference between the peak and nadir in activity and delayed rhythms as determined by the timing of peak activity during the day (e.g., acrophase) were associated with increased odds of developing dementia.

Further evidence that sleep disruption results in cognitive impairment has come from studies of individuals with sleep disordered breathing. In a prospective study of 298 women without dementia who had an overnight polysomnogram, 105 were found to have sleep disordered breathing as defined by an apnea-hypopnea index $\geq$15 events per hour of sleep and an associated risk of developing mild cognitive impairment or dementia (Yaffe et al., 2011). This finding was associated with oxygen desaturation and a high percentage of sleep time in sleep disordered breathing, but not sleep fragmentation or sleep duration. In another study, sleep fragmentation as measured by actigraphic changes in rest and activity has been demonstrated to result in poor cognitive function in the absence of sleep disordered breathing even when controlling for demographic factors, daily hours of rest, and total daily activity (Lim et al., 2012).

Recently published work also using actigraphy to monitor the sleep-wake cycle in cognitively normal individuals aged 45–75 years has shown decreased sleep efficiency and increased nap frequency in individuals with amyloid deposition compared with those similarly aged without amyloid deposition determined by CSF Aβ42 levels (Ju et al., 2013). These cognitively normal individuals with amyloid deposition most likely have preclinical AD and will develop cognitive impairment over time. The importance of this finding is that all individuals studied were cognitively normal but shared a statistically significant difference in sleep parameters when separated by amyloid deposition status, which supports the hypothesis that sleep disturbances are associated with AD pathology and precede the onset of cognitive impairment.

3. Aβ diurnal pattern

Because of the hypothesized role of Aβ in AD pathogenesis, the metabolism of Aβ in the brain has been investigated. Aβ concentrations in CSF have been shown to be stable over 10–18 months intervals in individuals with dementia of the Alzheimer's type (Andreasen et al., 1999; Kanai et al., 1998). Since CSF Aβ levels could potentially function as a biomarker to follow the effect of therapeutic drug trials in individuals with preclinical AD, a study measuring CSF Aβ levels over shorter time intervals was performed in 15 cognitively normal participants aged 23–78 years (Bateman et al., 2007). Serial CSF samples were collected every hour for 36 hours via indwelling lumbar catheter and Aβ concentrations were measured by enzyme-linked immunosorbent assay for Aβ40, Aβ42, and total Aβ. Significant variation in Aβ levels of 1.5–4 times were detected with Aβ40 and Aβ42 and total Aβ levels highly correlated over time indicating that they are likely regulated by similar processes.

To address the possible correlation between fluctuating Aβ concentrations and time of day or activity levels, a subsequent study collected serial CSF samples via lumbar catheter every hour for 36 hours while simultaneously monitoring sleep with ambulatory polysomnography and observing activity levels with video (Huang et al., 2012). Forty-six participants were enrolled in one of the following 3 groups: (1) young normal controls aged 18–60 years; (2) older adults age >60 years who were negative for amyloid deposition by PiB-PET; and (3) older adults aged >60 years age-matched to group 2 who were positive for amyloid deposition by PiB-PET. The hourly CSF concentrations of Aβ40 and Aβ42 were analyzed using cosinor analysis (Fig. 1). A cosine transformation was applied to the time variable using 24 hours as the default circadian cycle and the mesor, amplitude, and acrophase were calculated for each participant and averaged within each group. Both soluble Aβ40 and Aβ42 isoform concentrations fluctuated by 25% over the collection period and the fluctuations fit a cosine wave, which is consistent with a diurnal pattern. No correlation between Aβ

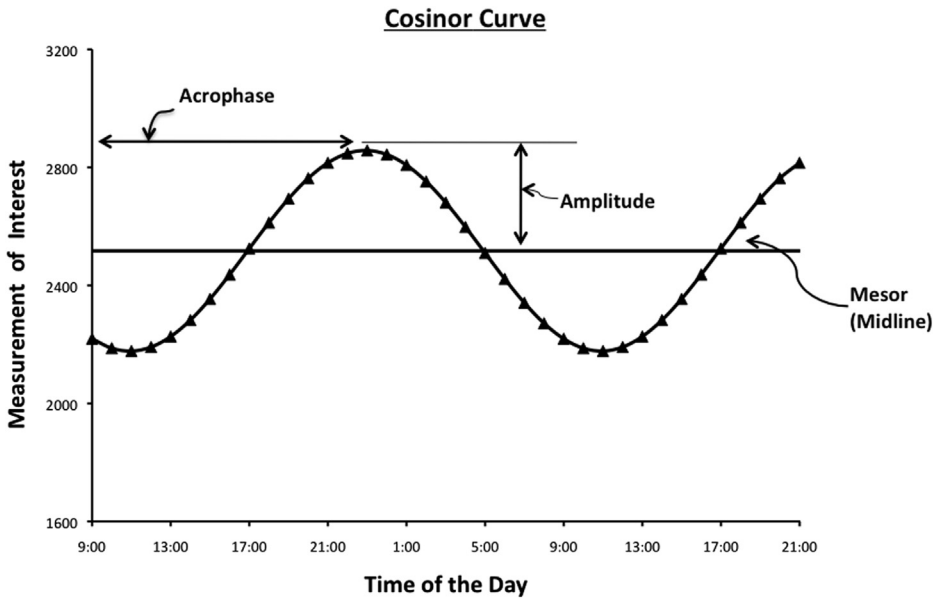

Fig. 1. Example of cosinor curve and terms used to describe a diurnal rhythm: mesor, midline of the oscillation; amplitude, distance between the peak and mesor; acrophase, and time corresponding to the peak of the curve or zenith.

fluctuation and activity levels was found, but soluble Aβ levels did fluctuate with the sleep-wake cycle after a 6-hour delay (Huang et al., 2012). Aβ40 and Aβ42 levels were higher in the CSF during wakefulness and lower during sleep. Further, the amplitude of the cosine wave decreased with age from young normal controls to individuals >60 years who were PiB-PET negative and the amplitude decreased more in individuals >60 years who were PiB-PET positive for amyloid deposition.

Studies in individuals with and without autosomal dominant AD mutations, (e.g., presenilin-1 and presenilin-2) replicate and extend the findings described previously regarding the Aβ diurnal pattern. The association between Aβ deposition and the decreased amplitude of the Aβ diurnal pattern has also been found in human subjects with presenilin mutations that cause familial AD. Individuals who were either presenilin mutation negative or mutation positive but negative for amyloid deposition by PiB-PET did not show attenuation of CSF Aβ diurnal rhythms, whereas individuals who were presenilin positive and positive for amyloid deposition did show attenuation (Roh et al., 2012). Further, a recent study modeling Aβ42 kinetics in presenilin mutation carriers versus noncarriers found that the fractional turnover rate of soluble Aβ42 relative to Aβ40 was faster in mutation carriers and correlated with amyloid deposition, which is consistent with increased deposition of Aβ42 into plaques leading to reduced recovery of Aβ42 in CSF (Potter et al., 2013). Extrapolating to sporadic AD, this finding may account for decreased Aβ42 levels in individuals with amyloid deposition. Aβ42 is more prone to aggregation into plaques and the plaques act as a "sink" sequestering Aβ42 once amyloid deposition has begun, thus preventing a rise in concentration over time.

The diurnal Aβ pattern has also been observed in animal models. APP transgenic mice (Tg2576) that develop amyloid deposition also show an association between the sleep-wake cycle and brain ISF Aβ concentrations (Kang et al., 2009), and soluble Aβ levels are higher in the ISF of APP transgenic mice during wakefulness and lower during sleep. These mice have normal sleep when they are young before amyloid deposition. However, once Aβ plaque formation in APP transgenic mice occurs, there is a loss of the Aβ diurnal pattern and, importantly, a markedly disrupted sleep-wake cycle with increased wakefulness and decreased sleep during the light phase when the mice would be expected to sleep (Roh et al., 2012). These observed changes in sleep in transgenic mice are completely prevented with active immunization of the mice with Aβ42 indicating that the abnormalities in sleep are because of Aβ aggregation in the brain. Finally, modification of sleep time in APP transgenic mice was investigated by Kang et al. (2009). Sleep deprivation for 21 days increased ISF Aβ concentrations and accelerated Aβ deposition into plaques, whereas enhancing sleep with an orexin receptor dual antagonist decreased Aβ aggregation into plaques (Kang et al., 2009).

4. Sleep, Aβ, and Alzheimer's disease pathophysiology: a proposed model

The diurnal Aβ pattern is hypothesized to be related to higher neuronal activity during wakefulness and decreased neuronal activity during sleep, such as occurs in SWS (Nir et al., 2011). Synaptic activity has been shown to increase ISF Aβ release from neurons in both the mouse and in humans (Brody et al., 2008; Cirrito et al., 2005). Loss of this diurnal pattern is likely because of sequestration of Aβ in extracellular amyloid plaques (e.g., altered clearance) or altered neuronal firing (e.g., altered production). There is evidence to support Aβ42 sequestration in plaques in older individuals with amyloid deposition that leads to decreased clearance and lower, less variable CSF Aβ42 concentrations. Production of soluble Aβ may be relatively increased during the sleep period by loss of SWS in the context of aging and/or sleep disturbances such as sleep apnea or insomnia. The net effect of these sleep changes is to increase wake time during the sleep period. More specifically, the DMN deactivates during sleep, particularly SWS (Samann et al., 2011). Therefore,

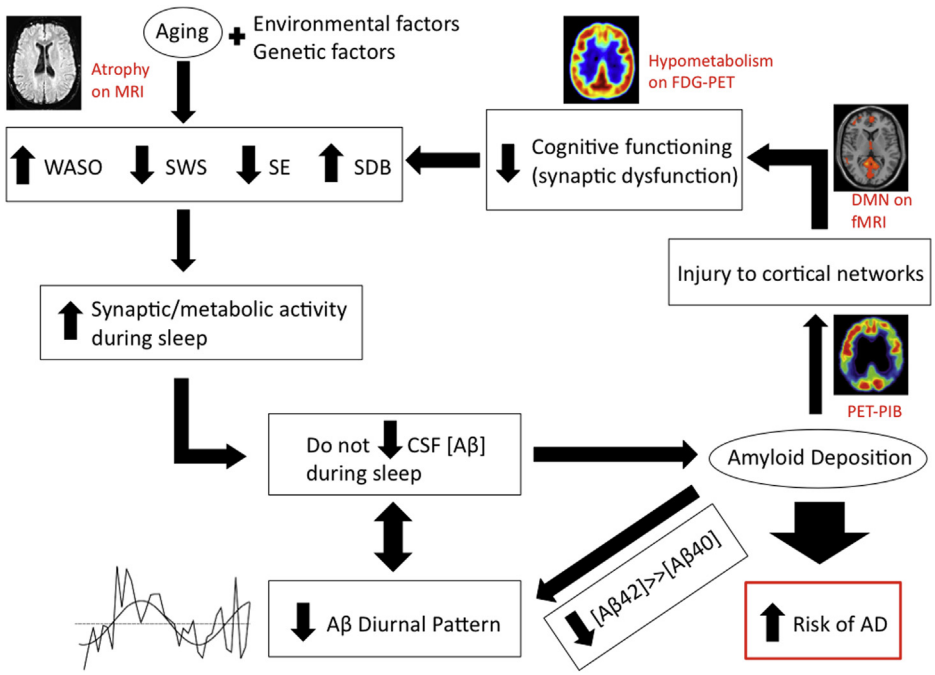

Fig. 2. Hypothetical model for the role of sleep in Alzheimer's disease pathogenesis. Abbreviations: Aβ, amyloid-beta; CSF, cerebrospinal fluid; DMN, default mode network; FDG, fluorodeoxyglucose; fMRI, functional MRI; MRI, magnetic resonance imaging; PET, positron emission tomography; PIB, Pittsburgh compound B; SE, sleep efficiency; SWS, slow wave sleep; SDB, sleep disordered breathing; WASO, wake after sleep onset.

decreased sleep efficiency and decreased SWS will lead to a lack of deactivation of the DMN, relative increases in synaptic and metabolic neuronal activity, increased soluble CSF Aβ levels during the sleep period, increased Aβ aggregation and sequestration into plaques, and attenuation of the Aβ diurnal pattern.

Although changes in the sleep-wake cycle have been associated with markers of AD pathology such as amyloid deposition, the timing, role, and extent of these changes that are associated with increasing stages of AD neuropathology and cognitive dysfunction is unclear. Findings in animal models hint that driving Aβ concentrations up or down with sleep deprivation or sleep induction, respectively, may affect amyloid aggregation into plaques. This finding has not been replicated in humans, but changes of Aβ production by 25%–40% (Jonsson et al., 2012) can completely protect or cause AD in humans (Jonghe et al., 1999), which suggests that increasing SWS time may decrease or prevent Aβ accumulation. Notably, a 25% change in Aβ concentration has been found between wakefulness and sleep (Huang et al., 2012). An alternative explanation of the current data is that sleep changes are a marker for progression of AD pathology rather than a key event in AD pathogenesis. Further research is needed to differentiate between these hypotheses.

A model for the role of sleep in AD pathogenesis is proposed to test future hypothesis-driven research (Fig. 2). As previously discussed, there are numerous changes that occur during aging including regional brain atrophy (e.g., medial prefrontal cortex) and changes in sleep parameters, that is, increased wake after sleep onset, decreased sleep efficiency, decreased SWS, and an increased incidence of sleep disorders (e.g., SDB). These changes occur in individuals with genetic and environmental risk factors that affect overall risk of AD. In individuals prone to AD based on these risk factors, sleep may play a more or less significant role in the development of AD.

The net effect of disturbed sleep parameters in older adults is a relative increase in synaptic and metabolic activity in the brain during the sleep period compared with younger individuals. Therefore, the concentration of Aβ in the CSF does not decrease during sleep as expected and results in attenuation of the Aβ diurnal pattern. Aβ concentrations during the sleep period are maintained at relatively high levels (25% higher than during sleep), which promotes amyloid deposition that may further feedback to disturb sleep and elevate Aβ levels during sleep.

The regions of the brain most at risk for amyloid deposition in this proposed model are those that are metabolically most active, that is, the DMN. Aβ deposition in brain regions is important because the DMN leads to network dysfunction, synaptic dysfunction, and impaired cognitive functioning. Impaired cognitive functioning and network dysfunction will manifest as hypometabolism or vice versa. Impaired cognitive function is associated with sleep disturbances, feeding back to the sleep changes associated with aging. The net effect is to increase Aβ deposition that is a known marker for AD risk.

5. Recommendations

The proposed model needs further research before recommendations regarding how to modify or improve sleep will mitigate the risk of future AD. However, there are 3 general guidelines that individuals may follow to promote restorative sleep.

1) Adequate sleep time needs to be allowed. For most individuals, this time is approximately 7–8 hours.
2) Maintaining a consolidated diurnal sleep pattern, ideally day and/or night, and avoiding sleep fragmentation will allow for appropriate cycling through sleep stages.
3) Sleep disorders such as sleep apnea should be evaluated and treated.

Disclosure statement

The authors have no conflicts of interest to disclose.

References

Alzheimer's Association, 2010. Changing the Trajectory of Alzheimer's Disease: A National Imperative, 2010. http://www.alz.org/documents_custom/trajectory.pdf. Accessed June 15, 2013.

Ancoli-Israel, S., Palmer, B.W., Cooke, J.R., Corey-Bloom, J., Fiorentino, L., Natarajan, L., Liu, L., Ayalon, L., He, F., Loredo, J.S., 2008. Cognitive effects of treating obstructive sleep apnea in Alzheimer's disease: a randomized controlled study. J. Am. Geriatr. Soc. 56, 2076–2081.

Andreasen, N., Hesse, C., Davidsson, P., Minthon, L., Wallin, A., Winblad, B., Vanderstichele, H., Vanmechelen, E., Blennow, K., 1999. Cerebrospinal fluid β-amyloid(1-42) in Alzheimer's disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease. Arch. Neurol. 56, 673–680.

Bateman, R.J., Wen, G., Morris, J.C., Holtzman, D.M., 2007. Fluctuations of CSF amyloid-β levels: implications for a diagnostic and therapeutic biomarker. Neurology 68, 666–669.

Bateman, R.J., Xiong, C., Benzinger, T.L., Fagan, A.M., Goate, A., Fox, N.C., Marcus, D.S., Cairns, N.J., Xie, X., Blazey, T.M., Holtzman, D.M., Santacruz, A., Buckles, V., Oliver, A., Moulder, K., Aisen, P.S., Ghetti, B., Klunk, W.E., McDade, E., Martins, R.N., Masters, C.L., Mayeux, R., Ringman, J.M., Rossor, M.N., Schofield, P.R., Sperling, R.A., Salloway, S., Morris, J.C., 2012. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N. Engl. J. Med. 367, 795–804.

Bero, A.W., Yan, P., Roh, J.H., Cirrito, J.R., Stewart, F.R., Raichle, M.E., Lee, J.M., Holtzman, D.M., 2011. Neuronal activity regulates the regional vulnerability to amyloid-β deposition. Nat. Neurosci. 14, 750–756.

Blackwell, T., Yaffe, K., Ancoli-Israel, S., Schneider, J.L., Cauley, J.A., Hillier, T.A., Fink, H.A., Stone, K.L., 2006. Poor sleep is associated with impaired cognitive function in older women: the study of osteoporotic fractures. J. Gerontol. A. Biol. Sci. Med. Sci. 61, 405–410.

Blackwell, T., Yaffe, K., Ancoli-Israel, S., Redline, S., Ensrud, K.E., Stefanick, M.L., Laffan, A., Stone, K.L., 2011. Association of sleep characteristics and cognition in older community-dwelling men: the MrOS sleep study. Sleep 34, 1347–1356.

Born, J., Wilhelm, I., 2012. System consolidation of memory during sleep. Psychol. Res. 76, 192–203.

Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82, 239–259.

Brody, D.L., Magnoni, S., Schwetye, K.E., Spinner, M.L., Esparza, T.J., Stocchetti, N., Zipfel, G.J., Holtzman, D.M., 2008. Amyloid-β dynamics correlate with neurological status in the injured human brain. Science 321, 1221–1224.

Buckner, R.L., 2004. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron 44, 195–208.

Buckner, R.L., Snyder, A.Z., Shannon, B.J., LaRossa, G., Sachs, R., Fotenos, A.F., Sheline, Y.I., Klunk, W.E., Mathis, C.A., Morris, J.C., Mintun, M.A., 2005. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J. Neurosci. 25, 7709–7717.

Cirrito, J.R., Yamada, K.A., Finn, M.B., Sloviter, R.S., Bales, K.R., May, P.C., Schoepp, D.D., Paul, S.M., Mennerick, S., Holtzman, D.M., 2005. Synaptic activity regulates interstitial fluid amyloid-β levels in vivo. Neuron 48, 913–922.

Cooke, J.R., Ayalon, L., Palmer, B.W., Loredo, J.S., Corey-Bloom, J., Natarajan, L., Liu, L., Ancoli-Israel, S., 2009. Sustained use of CPAP slows deterioration of cognition, sleep, and mood in patients with Alzheimer's disease and obstructive sleep apnea: a preliminary study. J. Clin. Sleep Med. 5, 305–309.

Faubel, R., Lopez-Garcia, E., Guallar-Castillon, P., Graciani, A., Banegas, J.R., Rodriguez-Artalejo, F., 2009. Usual sleep duration and cognitive function in older adults in Spain. J. Sleep Res. 18, 427–435.

Ferrie, J.E., Shipley, M.J., Akbaraly, T.N., Marmot, M.G., Kivimaki, M., Singh-Manoux, A., 2011. Change in sleep duration and cognitive function: findings from the Whitehall II study. Sleep 34, 565–573.

Greicius, M.D., Srivastava, G., Reiss, A.L., Menon, V., 2004. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc. Natl. Acad. Sci. U.S.A 101, 4637–4642.

Hardy, J., Selkoe, D.J., 2002. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297, 353–356.

Huang, Y., Potter, R., Sigurdson, W., Santacruz, A., Shih, S., Ju, Y.-E., Kasten, T., Morris, J.C., Mintun, M., Duntley, S., Bateman, R.J., 2012. Effects of age and amyloid deposition on Aβ dynamics in the human central nervous system. Arch. Neurol. 69, 51–58.

Jack, C.R., Knopman, D.S., Jagust, W.J., Shaw, L.M., Aisen, P.S., Weiner, M.W., Petersen, R.C., Trojanowski, J.Q., 2010. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 9, 119–128.

Jarrett, J.T., Berger, E.P., Lansbury, P.T., 1993. The carboxy terminus of the β amyloid protein is critical for the seeding of amyloid formation: implications for the pathogenesis of Alzheimer's disease. Biochemistry 32, 4693–4697.
Jonghe, C.D., Cras, P., Vanderstichele, H., Cruts, M., Vanderhoeven, I., Smouts, I., Vanmechelen, E., Martin, J.-J., Hendriks, L., Broeckhoven, C.V., 1999. Evidence that Abeta-42 plasma levels in presenilin-1 mutation carriers do not allow for prediction of their clinical phenotype. Neurobiol. Dis. 6, 280–287.
Jonsson, T., Atwal, J.K., Steinberg, S., Snaedal, J., Jonsson, P.V., Bjornsson, S., Stefansson, H., Sulem, P., Gudbjartsson, D., Maloney, J., Hoyte, K., Gustafson, A., Liu, Y., Lu, Y., Bhangale, T., Graham, R.R., Huttenlocher, J., Bjornsdottir, G., Andreassen, O.A., Jonsson, E.G., Palotie, A., Behrens, T.W., Magnusson, O.T., Kong, A., Thorsteinsdottir, U., Watts, R.J., Stefansson, K., 2012. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature 488, 96–99.
Ju, Y.-E., McLeland, J.S., Toedebusch, C.D., Xiong, C., Fagan, A.M., Duntley, S., Morris, J.C., Holtzman, D.M., 2013. Sleep quality and preclinical Alzheimer's disease. JAMA Neurol. 70, 587–593.
Kanai, M., Matsubara, E., Isoe, K., Urakami, K., Nakashima, K., Arai, H., Sasaki, H., Abe, K., Iwatsubo, T., Kosaka, T., Watanabe, M., Tomidokoro, Y., Shizuka, M., Mizushima, K., Nakamura, T., Igeta, Y., Ikeda, Y., Amari, M., Kawarabayash, i.T., Ishiguro, K., Harigaya, Y., Wakabayashi, K., Okamoto, K., Hirai, S., Shoji, M., 1998. Longitudinal study of cerebrospinal fluid levels of tau, Aβ1-40, and Aβ1-42(43) in Alzheimer's disease: a study in Japan. Ann. Neurol. 44, 17–26.
Kang, J.-E., Lim, M.M., Bateman, R.J., Lee, J.J., Smyth, L.P., Cirrito, J.R., Fujiki, N., Nishino, S., Holtzman, D.M., 2009. Amyloid-β dynamics are regulated by orexin and the sleep-wake cycle. Science 326, 1005–1007.
Keage, H.A.D., Banks, S., Yang, K.L., Morgan, K., Brayne, C., Matthews, F.E., 2012. What sleep characteristics predict cognitive decline in the elderly? Sleep Med. 13, 886–892.
Kronholm, E., Sallinen, M., Suutama, T., Sulkava, R., Era, P., Partonen, T., 2009. Self-reported sleep duration and cognitive functioning in the general population. J. Sleep Res. 18, 436–446.
Lim, A.S., Yu, L., Costa, M.D., Leurgans, S.E., Buchman, A.S., Bennett, D.A., Saper, C.B., 2012. Increased fragmentation of rest-activity patterns is associated with a characteristic pattern of cognitive impairment in older individuals. Sleep 35, 633–640.
Loerbroks, A., Debling, D., Amelang, M., Sturmer, T., 2010. Nocturnal sleep duration and cognitive impairment in a population-based study of older adults. Int. J. Geriatr. Psychiatry 25, 100–109.
Mander, B.A., Rao, V., Lu, B., Saletin, J.M., Lindquist, J.R., Ancoli-Israel, S., Jagust, W., Walker, M.P., 2013. Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. Nat. Neurosci. 16, 357–364.
Massimini, M., Huber, R., Ferrarelli, F., Hill, S., Tononi, G., 2004. The slow wave oscillation as a traveling wave. J. Neurosci. 24, 6862–6870.
Mayeux, R., Stern, Y., 2012. Epidemiology of Alzheimer disease. Cold Spring Harb. Perspect. Med. 2, a006239.
McCurry, S.M., Logsdon, R.G., Teri, L., Gibbons, L.E., Kukull, W.A., Bowen, J.D., McCormick, W.C., Larson, E.B., 1999. Characteristics of sleep disturbance in community-dwelling Alzheimer's disease patients. J. Geriatr. Psychiatry Neurol. 12, 53–59.
Meyer-Luehmann, M., Stalder, M., Herzig, M.C., Kaeser, S.A., Kohler, E., Pfeifer, M., Boncristiano, S., Matthews, P.M., Mercken, M., Abramowski, D., Staufenbiel, M., Jucker, M., 2003. Extracellular amyloid formation and associated pathology in neural grafts. Nat. Neurosci. 6, 370–377.
Mintun, M.A., LaRossa, G.N., Sheline, Y.I., Dence, C., Lee, S., Mach, R., Klunk, W.E., Mathis, C.A., DeKosky, S.T., Morris, J.C., 2006. [^{11}C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. Neurology 67, 446–452.
Morris, J.C., 2005. Mild cognitive impairment and preclinical Alzheimer's disease. Geriatrics, Suppl, 9–14.
Morris, J.C., Roe, C.M., Grant, E.A., Head, D., Storandt, M., Goate, A.M., Fagan, A.M., Holtzman, D.M., Mintun, M.A., 2009. PIB imaging predicts progression from cognitively normal to symptomatic Alzheimer's disease. Arch. Neurol. 66, 1469–1475.
Nir, Y., Staba, R.J., Andrillon, T., Vyazovskiy, V.V., Cirelli, C., Fried, I., Tononi, G., 2011. Regional slow waves and spindles in human sleep. Neuron 70, 153–169.
Potter, R., Patterson, B.W., Elbert, D.L., Ovod, V., Kasten, T., Sigurdson, W., Mawuenyega, K., Blazey, T., Goate, A., Chott, R., Yarasheski, K.E., Holtzman, D.M., Morris, J.C., Benzinger, T.L., Bateman, R.J., 2013. Increased in vivo amyloid-β42 production, exchange, and loss in presenilin mutation carriers. Sci. Transl. Med. 5, 189ra77.
Potvin, O., Lorrain, D., Forget, H., Dube, M., Grenier, S., Preville, M., Hudon, C., 2012. Sleep quality and 1-year incident cognitive impairment in community-dwelling older adults. Sleep 35, 491–499.
Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2000. A default mode of brain function. Proc. Natl. Acad. Sci. U.S.A 98, 676–682.
Redline, S., Kirchner, H.L., Quan, S.F., Gottlieb, D.J., Kapur, V., Newman, A., 2004. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. Arch. Intern. Med. 164, 406–418.
Roh, J.H., Huang, Y., Bero, A.W., Kasten, T., Stewart, F.R., Bateman, R.J., Holtzman, D.M., 2012. Disruption of the sleep-wake cycle and diurnal fluctuation of amyloid-β in mice with Alzheimer's disease pathology. Sci. Transl. Med. 4, 150ra22.
Samann, P.G., Wehrle, R., Hoehn, D., Spoormaker, V.I., Peters, H., Tully, C., Holsboer, F., Czisch, M., 2011. Development of the brain's default mode network from wakefulness to slow wave sleep. Cereb. Cortex 21, 2082–2093.
Sowell, E.R., Peterson, B.S., Thompson, P.M., Welcome, S.E., Henkenius, A.L., Toga, A.W., 2003. Mapping cortical change across the human life span. Nat. Neurosci. 6, 309–315.
Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., Iwatsubo, T., Jack, C.R., Kaye, J., Montine, T.J., Park, D.C., Reiman, E.M., Rowe, C.C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M.C., Thies, B., Morrison-Bogorad, M., Wagster, M.V., Phelps, C.H., 2011. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute of Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 7, 280–292.
Strooper, B.D., Vassar, R., Golde, T., 2010. The secretases: enzymes with therapeutic potential in Alzheimer disease. Nat. Rev. Neurol. 6, 99–107.
Tononi, G., Cirelli, C., 2006. Sleep function and synaptic homeostasis. Sleep Med. Rev. 10, 49–62.
Tranah, G.J., Blackwell, T., Stone, K.L., Ancoli-Israel, S., Paudel, M.L., Ensrud, K.E., Cauley, J.A., Redline, S., Hillier, T.A., Cummings, S.R., Yaffe, K., 2011. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Ann. Neurol. 70, 722–732.
Tworoger, S.S., Lee, S., Schernhammer, E.S., Grodstein, F., 2006. The association of self-reported sleep duration, difficulty sleeping, and snoring with cognitive function in older women. Alzheimer's Dis. Assoc. Disord. 20, 41–48.
Vlassenko, A.G., Vaishnavi, S.N., Couture, L., Sacco, D., Shannon, B.J., Mach, R.H., Morris, J.C., Raichle, M.E., Mintun, M.A., 2010. Spatial correlation between brain aerobic glycolysis and amyloid-β (Aβ) deposition. Proc. Natl. Acad. Sci. U.S.A 107, 17763–17767.
Vyazovskiy, V.V., Olcese, U., Hanlon, E.C., Nir, Y., Cirelli, C., Tononi, G., 2011. Local sleep in awake rats. Nature 472, 443–447.
Xu, L., Jiang, C.Q., Lam, T.H., Liu, B., Jin, Y.L., Zhu, T., Zhang, W.S., Cheng, K.K., Thomas, G.N., 2011. Short or long sleep duration is associated with memory impairment in older Chinese: the Guangzhou biobank cohort study. Sleep 34, 575–580.
Yaffe, K., Laffan, A.M., Harrison, S.L., Redline, S., Spira, A.P., Ensrud, K.E., Ancoli-Israel, S., Stone, K.L., 2011. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 306, 613–619.
Yesavage, J.A., Friedman, L., Ancoli-Israel, S., Bliwise, D., Singer, C., Vitiello, M.V., Monjan, A.A., Lebowitz, B., 2003. Development of criteria for defining sleep disturbance in Alzheimer's disease. J. Geriatr. Psychiatry Neurol. 16, 131–139.